UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,457	08/27/2003	Ronald G. Crystal	216474	5783

23460 7590 05/19/2006

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER	
NOBLE, MARCIA STEPHENS	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,457	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-21* is/are pending in the application.

4a) Of the above claim(s) *11,12 and 22-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/27/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's election with traverse of Group II, claims 1-10 and 13-21with a species election of protective antigen for the exotoxin and a lysosomal pathway for the subcellular sorting pathway, in the reply filed on 4/24/06 is acknowledged. The traversal is on the ground(s) that the subject matter between the groups and species election are overlapping and therefore no a serious search burden. This is not found persuasive because the search of the different groups would be considered a search burden because the search strategy would be different even though they are classified together. Because of the significant reliance upon the non-patent literature in examination of the biotechnology art, applications are rarely searched by classification and are more commonly search by terminology; therefore search burden is based upon additional or different terms that must be added to the search query. In the instant case, additional terms like non-viral, non-viral gene therapy, viral gene therapy, EF, LF, extracellular pathway, cytoplasmic pathway, degradative pathway, etc would each need added as individual search queries and these would each need to be search in several different databases, therefore resulting in multiple additional searches. This level of additional search is consider undue and would be considered a search burden for the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11, 12, and 22-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/24/06.

Claims 1-10 and 13-21 are under consideration.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed on 8/27/2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

2. The disclosure is objected to because of the following informalities: a hyperlink present in the specification on p 26 [0071].

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-10 and 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "codons expressed ***more frequently*** in humans". The terminology, "more frequently" is relative terminology which renders the claim indefinite. The terminology, "more frequently" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds are not clear because it is not clear to what degree the codons need to be to be altered to attain "more frequently" expressed or how many of the codons need to be optimized for human expression than those of *Bacillus anthracis*. Furthermore, if the exogenous protein can be expressed in its native form by humans, would these not be optimized for human expression?

Claims 2-20 and 13-21 are directly or indirectly dependent on claim 1 which has been deemed indefinite, therefore these dependent claims are also rendered indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-10 and 13-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. (1999, of record), Wu et al (1995; of record), Farina et al (2001, of record), Mogridge et al (2001; of record), and Hamdan et al (Parasitol Res. 88:583-586, June 2002).

The instant invention is drawn to a chimpanzee replication-deficient adenoviral gene transfer vector comprising a nucleic acid sequence which encodes at least an immunogenic portion of protective antigen (PA) of *Bacillus anthracis* and a heterologous sorting signal, lysosomal-associated membrane protein 1 (LAMP-1), wherein the nucleic acid sequence comprises codons expressed more frequently in humans than in *Bacillus anthracis*. Narrowing embodiments specify that the nucleic acid sequence encode an oligomerization mutant of PA, that the LAMP-1 direct the exotoxin to a lysosomal pathway, and that the gene transfer vector transduce antigen presenting cells (APC).

Gu et al teach a DNA plasmid vaccine encoding the immunogenic and biologically active portion of PA which encodes for AA 173-764 of PA (abstract and p. 341, col1, par 2). Because of the breadth of the claims and the indefinite nature of the recitation,"codons expressed more frequently in humans than *Bacillus anthracis*, the broadest reasonable interpretation of the claims would allow for the native sequence to be used if it can be expressed in the human and is immunogenic in the human.

Therefore, the PA sequence taught by Gu et al encompass the limitations of the instant claims. Gu et al also teach a need for the development of better anthrax vaccines that have improved safety profiles and immunogenicity and that do not trigger undesirable local reactogenicity (p. 340, col 3, par 10). Gu et al. do not teach a LAMP-1 sequence that direct the PA to the lysosomal pathway of APC cells, an adenoviral vector for delivery of the sequence, an oligomerization mutant of PA, nor codons that more frequently express in humans.

Wu et al teach a viral vector vaccine encoding the LAMP-1 signal peptide, the HPV16 E7 gene sequence and LAMP-1 sorting signal (par bridging 11671 and 11672, and Fig 1, on p. 11672). This vector was effectively expressed and the chimeric protein was directed to the lysosomal compartments and lead to enhances MHC II presentation on APC (p. 11674, col 2, lines 4-11). Wu et al also teach that the use of this type of sequence and expression approach to vaccination provides for improved vaccine potency and potentially very effective vaccines against HPV in the instant case and in general vaccine design (abstract, p. 11671, col 1 par 1, col2 par 2 &3, p. 1165 last par). Wu et al does not teach a PA sequence, an adenoviral vector for delivery of the sequence, an oligomerization mutant of PA, nor codons that more frequently express in humans.

Farina et al teach a replication-defective virus called C68 that was developed for gene transfer or as a vaccine carrier (see Materials and Methods for C68 disclosure). Farina et al also teach that this vector was generated to circumvent problems that arise because of existing immunity as a result of a naturally acquired adenoviral infection as

seen with other vectors used for gene transfer or vaccine carrier (p. 11603 par bridging col 1 & 2, p. 1161, col 2 par 2). Farina et al also teach its improved utility as a vector because it does not result in neutralizing antibodies that can interfere with delivery (p. 11612, col 1, par 2). They also indicate that preliminary results indicate that the vector is functioning as an excellent vaccine carrier for HIV and rabies (p. 11612, last par). Farina et al do not teach a PA sequence, a LAMP-1 sequence that direct the PA to the lysosomal pathway of APC, an oligomerization mutant of PA, nor codons that more frequently express in humans.

Mogridge et al teaches a sequence encoding mutated form of amino acid sequence 510-518 of domain 3 of the PA that impair heptamerization of PA_{63} and are also defective in their ability to bind LF and/or EF and therefore that these mutants are oligomerization deficient and result in impaired oligomerization necessary to the toxic effect of the exotoxins on cells (p. 2111, col 2 , par 2 and Table 1 p. 2113). This disclosure of the pivitol role that domain 3 plays in the demonstrates its importance in the function of all three exotoxins and there toxic impact on cells. It also provides motivation for use as an a vaccine because it not only impairs the PA which is the most common target of anthrax vaccines. It also affects the other exotoxins involved and therefore targets the whole machinery of the toxin, therefore making it a more effective target for vaccine design. Mogridge et al. does not specifically teach the sequence use in a DNA vaccine vector.

Hamdan et al teach a method of redesigning *S. manosoni* cDNA using recursive PCR and preferred human codons without changing without changing the amino acid

sequence encoded by the gene of interest, SmGPCR (p. 584, col 1, par 1). Hamdan et al teach that this approach dramatically increased the expression of the gene in human HEK 293 cells and suggest that codon optimization is a valuable method for improving heterologous expression of non-human genes in human cells (see abstract).

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify a gene transfer vector in all the ways discussed in the art to provide for an improved vector for vaccination against anthrax toxin. Gu et al demonstrated that DNA vaccine vectors against PA were established and that more development for improved vectors was needed. Wu et al demonstrated and taught that one approach to improve a vaccine is via presentation of the antigen on APC cells and that their LAMP-1 sequence could effectively do so for presenting antigens such as PA. Farina et al suggest a vector that would improve the deliver and act as a efficient vaccine carrier in human with out the negative immunological side effects associated with viral vector delivery. Mogridge et al provide a sequence for PA that is a key player in the assemble and effect of all three exotoxin making it a prime target for vaccine to not only neutralize PA but impair binding of LF and/or EF, which is necessary for their toxic function. Furthermore, the expression of the mutant should be safer in vivo to humans because it is defective and non-functional. Hamden et al provide for means to optimize expression of the antigen, PA in human cells to assure robust expression of PA to induce an immune response. Furthermore, it also would have been obvious to an artisan of ordinary skill to combined all of these components with a reasonable expectation of success because methods of producing vectors are by PCR are well established in the art and the

success of these approaches and the motivation to incorporate them were also present in the art as well.

Relevant Art

5. The instant invention has been disclosed in post-filing art by the inventors demonstrating reduction to practice (Tan et al. Hum Gene Therapy 14:1673-1682, 11/23/2003).

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcia S. Noble

Joe Woitach
AU 1632